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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

SAOUD, CHRISTINE J

ART UNIT	PAPER NUMBER
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1647

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12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/345,373

Applicant(s)
RUBEN et al.

Examiner
Christine Saoud

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Sep 4, 2001
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 43-45 and 94-182 is/are pending in the application.
- 4a) Of the above, claim(s) 43-45, 94-126, and 135-182 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 127-134 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- *See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____

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DETAILED ACTION

Restriction Requirement:

Applicant's election with traverse of the sequence of SEQ ID NO:2, residues 69-208 in Paper No. 11, filed 04 September 2001 is acknowledged. It is noted that Applicant refers to "election of 'species'". Applicant is reminded that a restriction requirement was made in paper #9, and this should not be construed as an election of species as asserted in the instant reply.

The traversal is on the ground(s) that (a) the Examiner has not shown that examination of the entire invention would present a serious search burden, (b) that the Examiner has not disclosed any statutory or regulatory basis for requiring the election of an individual sequence within the previously elected Group I, (c) that the current restriction represents a restriction within a Markush group, and that said Markush group has members that are sufficiently few in number and very closely related, so that a search of all members may be made without a serious burden, and (d) that the Examiner has not addressed MPEP 804.03, directed to nucleotide sequences, in which the Commissioner authorized a partial waiver of restriction practice, allowing the examination of up to ten sequences, and further traversing that the instant nucleic acids encode different fragments of the same protein, rather than different proteins. These arguments are not found persuasive because:

With respect to point (a) above, the Examiner explained clearly why the multitude of claimed polypeptides comprising a specific sequence present a serious search burden in the presentation of the requirement in paper #9. Spanning pages 2-3, the Examiner explained

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“[a]lthough the classifications for these various polypeptides are overlapping, for instance 530/350, each represents a patentably distinct product with distinct physical and functional characteristics. Further the search for more than one product would be burdensome, because each polypeptide requires a search of the corresponding region of SEQ ID NO: 2 which requires a separate “word search” of the polypeptide databases, or by claiming polypeptides which have percent identity to a disclosed polypeptide, which requires a broader search of the polypeptide databases.”

With respect to point (b) above, the statutory basis for this requirement is U.S.C. 121. The Examiner regrets failing to make this clear in the previous Office Action.

With respect to point (c) above, that the current restriction represents a restriction within a Markush group, and that said Markush group has members that are sufficiently few in number and very closely related, so that a search of all members may be made without a serious burden, the Examiner notes MPEP 803.02, which states:

If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all claims on the merits, even though they are directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require restriction.

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Since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas*, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. *In re Harnish*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility.

In this case, the first requirement is not met, in that the members of the group are not sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden. Specifically, the instant claims encompass at least 16 distinct sequence searches, wherein the resources of the Patent Office only permit for the search of a single sequence, not including the breadth of the claims when % identity is taken into account. With respect to the search burden that this presents, see the discussion of point (a), above.

Further, contrary to the second paragraph quoted from the MPEP above, there is no unity of invention here, as no common utility has been presented, and there is no substantial structural feature disclosed as being essential to that utility; such would seem impossible, as the claimed fragments are, in many cases, non-overlapping, and thus do not share *any* structural feature.

Applicant's comments regarding "allowance of a generic claim" and entitlement to additional "species" are misplaced in that a species election was not required, but rather a restriction of invention.

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Finally, with respect to applicant's point (d), that the Examiner has not addressed MPEP 803.04, directed to nucleotide sequences, in which the Commissioner authorized a partial waiver of restriction practice, allowing the examination of up to ten sequences, and further traversing that the instant nucleic acids encode different fragments of the same protein, rather than different proteins. First, the instant claims are directed to polypeptides, and not nucleotide sequence. Secondly, the issue in question was a partial waiver of restriction practice to allow examination of up to ten nucleic acid sequences. This waiver was issued in 1996. Since then, the nucleic acid and protein databases that must be searched for each of the independent and distinct sequence claimed herein have multiplied many fold in size, such that it is now burdensome to search more than a single sequence in an application. Further, the waiver allowed, but did not require the Examiner to search ten sequences. With respect to applicants second point, it is not true that the claimed nucleic acids merely encode different fragments of the same protein, rather than different proteins. As many of the fragments are quite short, and could be embedded within other patentably distinct proteins, it cannot be said that they are merely fragments of a common protein, and a separate search is required for each possible fragment.

The requirement is still deemed proper and is therefore made FINAL.

The elected invention is nucleic acids which encode SEQ ID NO: 2, residues 69-208. Thus, claims 43-45, 94-126, and 135-182 are withdrawn from prosecution as being drawn to a non-elected invention. Claims 127-134 are under examination as these are the claims indicated by Applicant to read on the elected invention (Applicant is reminded that the restriction that was presented in paper #9 was NOT an election of species, but rather a restriction requirement to distinct inventions. Further reference to "election of species" is discouraged.)

Claim Rejections - 35 USC § 112

1. Claims 127-134 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising an amino acid sequence

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identical to Ser (69) - Ser (208) of SEQ ID NO:2, does not reasonably provide enablement for polypeptides having 90-97% amino acid sequence identity to said sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to polypeptides which have 90-97% sequence identity to a portion of the amino acid sequence of SEQ ID NO:2 (residues 69-208). However, the instant specification teaches a single embodiment of the claimed invention which is a polypeptide that has the amino acid sequence of SEQ ID NO:2 or a deletion of the first 33 amino acids (predicted signal sequence removed). In order to use the claimed invention, the polypeptides which are claimed would need to retain the activity (immunogenic or biological) of the polypeptide which has the amino acid sequence of SEQ ID NO:2 in order for one of ordinary skill to use what is claimed. The instant specification provides no guidance as how to modify the disclosed polypeptide and obtain a protein which has the activity of the native polypeptide (SEQ ID NO:2). The specification provides no guidance as to which amino acids (i.e. structural elements) of the native proteins are critical to the biological/immunological activity or which amino acids could be altered without destroying these activities. Without this type of guidance, the skilled artisan does not have a reasonable expectation of making a polypeptide which has any amino acid variation from the disclosed polypeptide and obtaining a functional protein that retains the activity of the native protein, which is necessary for one to use the claimed invention. One may argue screening for activity could be done, however, this is basically a "wish to know" and the standard for an enabling disclosure is not one of making and testing. In so far as the instant claims encompass a polypeptide having a sequence other than the disclosed sequence identified above, specific case law bears on this issue: Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd., 18 U.S.P.Q. 2d, 1016, held that;

"A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and describe how to obtain it. *See Oka*, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur

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unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated.”

The fact pattern is directly analogous in that what is claimed are polypeptides that have yet to be isolated or characterized for the activity recited in the application and thereby constitutes a “wish to know” rather than a reduction to practice, absent evidence to the contrary. The decisions of *In re Fisher*, Amgen Inc. v. Chugai, and *In re Wands* have been relied upon in the instant rejection (see below) and by the court in a recent CAFC decision, Genentech, Inc. V. Novo Nordisk, 42 USPQ2d, 100 (CAFC 1997) because they show that the judicial interpretation of the first paragraph of 35 U.S.C. § 112 requires that the breadth of the claims must be based upon the predictability of the claimed subject matter and not on some standard of trial and error. To argue that one can make material embodiments of the invention and then test for those that work in the manner disclosed or that the instant claims only encompass the working embodiments is judicially unsound. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not without actually making and testing them, then the instant application does not support the breadth of the claims.

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The issue is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. This position is consistent with the decisions in *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) and Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd., 13 USPQ2d, 1737 (1990) and In re Wands, 8 USPQ2d, 1400 (CAFC 1988). The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims.

The state of the art is such that it is acknowledged that amino acid modifications of proteins is unpredictable. One cannot merely predict protein function from amino acid sequence information or from amino acid sequence similarity to other related proteins. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990,

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Science 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure, pp. 14-16). Robson et al. state "the changing of one amino acid in a sequence gives, by definition, a new protein. Although this definition is sometimes waived, it is dangerous to do so because it cannot be assumed a priori that changing even one amino acid will not significantly, perhaps even drastically, alter the properties of a protein." The instant claims encompass polypeptides which differ from the native polypeptide by the substitution, insertion, deletion or modification of as many as 14 amino acids. However, Applicant has provided no guidance beyond the mere disclosure of a single, naturally occurring protein to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions, insertions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification provides a biological assay for screening for active muteins, this is not adequate guidance as to the nature of the polypeptides that may be constructed, but is merely an invitation to the artisan to use the disclosed protein as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

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Due to the large quantity of experimentation necessary to generate the large number of polypeptides encompassed by the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues in the disclosed polypeptide which are required for the functional and structural integrity of the protein. It is this additional characterization of the protein that is required in order to obtain the functional and structural data needed to permit one to produce a protein which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

Conclusion

2. Claims to an isolated polypeptide comprising an amino acid sequence identical to Ser (69)
 - Ser (208) of SEQ ID NO:2 are free of the prior art of record.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 7AM to 3PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556. If this number is out of service, please call the Group receptionist for an alternate number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

November 13, 2001

CHRISTINE J. SAOUD
PRIMARY EXAMINER

Christine J. Saoud